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Epidemiology of Osteochondrodysplasias: Changing Trends Due to Advances in Prenatal Diagnosis

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The osteochondrodysplasias (skeletal dysplasias) are a heterogeneous group of disorders characterized by abnormalities in cartilage and bone growth and development. Some of these disorders are detectable during the second trimester by sonographic techniques. We ascertained cases of osteochondrodysplasias in elective pregnancy terminations, stillborn infants older than 20 gestational weeks, and liveborn infants diagnosed by the fifth day of life as part of an ongoing active malformation surveillance program. Forty-nine cases of osteochondrodysplasias were identified among approximately 126,000 deliveries at Brigham and Women's Hospital (BWH) during a 15-year period (Feb. 16, 1972–Feb. 15, 1975; Jan. 1, 1979–Dec. 31, 1990). When cases delivered to women who had planned to deliver at another hospital but were transferred for high-risk care (transfers) were excluded, the prevalence rate was 2.14 cases per 10,000 deliveries. During the early period (1972–1975) no cases were suspected prenatally, while during the 1988–1990 period, 80% of all cases and 57% of cases delivered to women who had always planned to deliver at BWH (non-transfers) were suspected by ultrasonography. Birth status changed through our period of surveillance. In the final 3-year period (1988–1990), 40% of all cases and 29% of non-transfers with osteochondrodysplasias were pregnancy terminations, compared to none during the 1972–1975 period. The increasing frequency of pregnancy terminations complicated the diagnosis of these conditions. Despite extensive evaluation, a definitive diagnosis was not possible in 8 of 49 cases (16%). Biochemical and molecular genetic methods of diagnosis will continue to become more important if the current trend of wide utilization of prenatal sonography and termination of affected pregnancies continues.

KEY WORDS: **osteochondrodysplasias, skeletal dysplasias, dwarfism, chondrodysplasias, fetus, bone, collagen diseases, prenatal diagnosis, ultrasonography**

INTRODUCTION

The osteochondrodysplasias (skeletal dysplasias) are a heterogeneous group of conditions characterized by abnormalities of cartilage and bone growth and development. The first midtrimester diagnosis of an osteochondrodysplasia, the Ellis-van Creveld syndrome, occurred in 1977 using ultrasound and fetoscopy [Mahoney and Hobbins, 1977], and more than 20 different types have subsequently been identified in the second trimester [Lachman, 1994]. Initially these diagnoses were made in fetuses at risk of an abnormality because of a family history. However, as ultrasonography has become a more routine component of prenatal care, the diagnosis of these conditions has become more

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common in families without a previous affected infant. Prenatal diagnosis of the osteochondrodysplasias not only introduces the option of elective termination of pregnancy, if the family desires, but also allows for optimal perinatal care when the pregnancy continues to delivery. Although the recognition of an osteochondrodysplasia is fairly reliably accomplished using ultrasonography, making a precise diagnosis is more difficult [Vandenburghe et al., 1984; Donnenfeld and Mennuti, 1987; Winter et al., 1988; Escobar et al., 1990]. However, a precise diagnosis is needed for the counseling of families regarding prognosis and risks and options in future pregnancies. We report our experience with the osteochondrodysplasias ascertained in 126,316 deliveries during a 15-year period at Brigham and Women's Hospital (BWH) in Boston, Massachusetts, and the effects of increasing prenatal identification on the epidemiology of these conditions.

METHODS

Fetuses and infants with osteochondrodysplasias were ascertained through an active malformation surveillance system at Brigham and Women's Hospital (BWH) (previously Boston Hospital for Women, Lying-In Division) by staff members who made frequent visits to the newborn and intensive care nurseries, pregnancy termination service, and pathology service to ask nurses, pediatricians, and pathologists to identify all potential cases. In addition, the findings of the pediatricians' examinations included in the medical records were reviewed sporadically in the early years and consistently since 1982 [Nelson and Holmes, 1989]. Cases were identified among liveborn and stillborn infants of at least 20 weeks' gestational age, and terminations of pregnancy during a 15-year period at BWH. Only cases identified or suspected before discharge from the nursery or before the fifth day of life were tabulated; abnormalities identified after the fifth day were excluded to allow for uniform case ascertainment (selection of the fifth day of life was based on the routine length of stay for a well newborn following a vaginal delivery at onset of the study; this had decreased to about 2 days by the end of the study). The 15 years of surveillance included 3 years between February 16, 1972, and February 15, 1975, and 12 years between January 1, 1979, and December 31, 1990.

Osteochondrodysplasias were defined as abnormalities of cartilage and/or bone growth and development, included in the International Nomenclature of Constitutional Diseases of Bone as well as other unclassifiable conditions fitting the definition [Spranger, 1992]. In a large proportion of cases, prenatal ultrasonography had been performed, either at BWH, other hospitals or at private ultrasound diagnostic facilities, and whenever possible, written reports of these studies were reviewed. In all cases in which the pregnancy ended in termination, stillbirth, or neonatal death, an autopsy was performed in the Department of Pathology at BWH, except for one infant who died at The Children's Hospital (Boston, MA) and whose autopsy was performed there. Pathology evaluations (gross and microscopic) and subsequent clinical evaluations in genetics clinics were reviewed. Radiographic examination had been performed on all cases except 3 (all pregnancy terminations). Diagnoses were made by geneticists, pathologists, and radiologists at BWH and The Children's Hospital, sometimes with consultation of outside experts; therefore, specific information regarding the basis on which the diagnosis was made was not available. The findings in the cases in which no specific diagnosis had been made by the above protocol were reviewed by 2 of us (RSL and DLR) in a further attempt to establish a specific diagnosis.

To allow for comparison of our birth rate to other studies which evaluated only lethal conditions, we classified each case as "lethal" or "nonlethal." An earlier classification delineated in the International Nomenclature of Constitutional Diseases of Bone (Revision, May, 1983) divided osteochondrodysplasias into 3 categories, and the first category, defects of growth of tubular bones and/or spine, was divided into conditions usually lethal before or shortly after birth and usually non-lethal dysplasias. We classified patients with known conditions considered lethal by this categorization, as well as patients with osteogenesis imperfecta (OI) type II, as lethal. For cases with undiagnosed conditions, those who were stillborn or died neonatally were considered lethal. Pregnancy terminations in which no final diagnosis was made were considered non-lethal, since it was unclear if these conditions were definitely lethal.

Because BWH is a tertiary care center, the transfer status of the mother of each case was determined; if she intended to deliver elsewhere, but was transferred to this hospital for high-risk care, she was considered a "transfer." Mothers who had planned to deliver at BWH were considered "non-transfers." The status of each mother with regard to transfer status was determined either from a review of her medical record or for some mothers by interviewing either the mother or her obstetrician.

Since the actual number of transfers among all mothers delivering at BWH was not known, prevalence rate determination used as a denominator the total number of livebirths and stillbirths greater than 20 weeks delivered at BWH, plus 10% of the pregnancy terminations performed at the hospital (this assumes that an estimated 10% of women who terminated pregnancies planned to deliver at BWH) [Limb and Holmes, 1994]. Thus defined, there was a total of 126,316 deliveries in the time period studied.

Controls for analysis of maternal and paternal age were obtained from cases collected between August 1, 1986, and December 31, 1990, as part of another study [details of case collection included in Holmes et al., 1994]. Maternal age was available on 874 cases, and paternal age was available on 610 cases. These cases were collected from 5 Boston area hospitals, but most were from BWH. The Student's t-test was used for statistical analysis, and statistical significance was defined as a P value < 0.05.

RESULTS

Forty-nine cases of osteochondrodysplasias were ascertained among 126,316 deliveries over the 15-year period. Of these, the mothers of 22 of 49 cases (45%)

were transferred to BWH; 20 of these were transferred because of a suspected fetal abnormality, and 2 were transferred because of impending premature delivery. These transfers were excluded for determination of rates. Therefore, prevalence, based on the remaining 27 cases among a total of 126,316 deliveries over the 15-year time period, was 2.14 cases per 10,000 deliveries (Table I). Twelve non-transfer cases were considered lethal, yielding a prevalence rate for these conditions of 0.95 per 10,000 births. Among all cases, 27 of 49 (55%) had conditions considered lethal.

The most common type of osteochondrodysplasia in our series was thanatophoric dysplasia, with a prevalence rate of 0.40 cases per 10,000 deliveries (Table II). OI type II represented the second most commonly diagnosed condition with a prevalence rate of 0.24 cases per 10,000 deliveries. If all cases of OI (types II and III) are included, the prevalence rate was 0.40 per 10,000 deliveries.

Eight (16%) of our 49 cases of osteochondrodysplasias remained without a specific diagnosis despite extensive studies and review (Table III). Of these cases, one was alive, had full radiographic studies and was seen in consultation as an in-patient, as well as in genetics clinic for evaluation. Of the remaining 7, all had autopsies performed, including gross and microscopic studies, and 7 of 8 had radiographic studies.

Four of the 8 patients in whom no diagnosis was made had cytogenetic studies performed, and all of these had normal karyotypes. Overall, cytogenetic studies were performed in about half (23 of 49) of our patients, and no abnormalities were found.

Of the 49 cases, 19 were males, 26 were females, and in 4 cases sex could not be determined, because of the destructive procedure used for pregnancy termination. Thus, the male:female sex ratio was 0.73:1. In the non-transfer group, there were 11 males, 14 females and 2 of undetermined sex, giving a male:female sex ratio of 0.79:1. In the 48 cases in which race was known, 42 were "white" and 6 were "non-white" (7:1). Of the non-transfer cases, 22 were considered "white" and 4 cases were "non-white" (5.5:1).

Maternal age was known on all patients, and the average was 28.5 years. Mean maternal age for non-transfer patients was 29.7 years. Mean maternal age for the control group was 29.2 years, and the age in our case group was not significantly different from that of the controls. Paternal age was known in 40 of the 49 cases; average paternal age was 31.3 years. Mean paternal age for the non-transfer group was 32.4 years. Mean paternal age for the control group was 32.7 years, not significantly different from that of the cases. Mean maternal age for thanatophoric dysplasia was 31.0 years, and mean paternal age was 32.7 years. For OI type II, mean maternal age was 25.3 years and mean paternal age was 27.7 years. These mean ages were not significantly different from the mean ages of the controls.

Family history was remarkable in 5 cases. In the male patient with Melnick-Needles syndrome, the mother was also affected [this infant was reported by Von Oeyen et al., 1982]. The parents who terminated a fetus with diastrophic dysplasia previously had an infant with this condition. The infant diagnosed with Larsen syndrome had 2 previously affected sibs and the parents were first cousins once removed. A stillborn patient with Desbuquois syndrome had one affected sib and the parents were second cousins. The parents of an infant with an osteogenesis imperfecta-like condition and encephalocele, a previously undescribed disorder, were first cousins.

Osteochondrodysplasias were identified frequently through the use of prenatal ultrasonography (Table IV). When evaluating all cases (including transfers), the percent of cases in which the diagnosis was suspected by prenatal ultrasound was 73% (36 of 49 cases). This increased from 0% during the 1972–1975 time period, to 50% during the 1979–1981 period, to 80% during the 1988–1990 time period. In the non-transfer group, 56% (15 of 27 cases) were suspected by ultrasound. As with the total cases, the proportion increased through the years. A similar trend was seen for cases suspected at or before 24 weeks gestation (Table IV).

Ultrasound examinations were performed during the second or third trimester in 42 of 49 cases (86%). Most cases in which no second or third trimester ultrasound examination had been done were delivered in the early years of the study (3 cases in the 1972–1975 time period, 3 cases in the 1979–1981 time period, and one case in the 1988–1990 time period). Among the 42 cases in which ultrasound study had been performed during the latter two-thirds of pregnancy, there were 6 cases in which an osteochondrodysplasia was not suspected. Four of these cases were considered to be non-lethal, while 2 were considered to be lethal. These include a case of thanatophoric dysplasia (ultrasound study in

TABLE I. Number of Cases (Total and Non-Transfers) and Prevalence Rate of Osteochondrodysplasias by Time Period

Time period	Total cases	Non-transfers	Number of deliveries	Rate per 10,000 deliveries[a]
1972–1974[b]	3	3	18,155	1.7
1979–1981	8	6	21,436	2.8
1982–1984	10	3	25,218	1.2
1985–1987	13	8	30,217	2.7
1988–1990	15	7	31,290	2.2
Totals	49	27	126,316	2.1

[a]Based on non-transfer cases.
[b]February 16, 1972–February 15, 1975.

TABLE II. Specific Types of Osteochondrodysplasias Diagnosed

Diagnosis	No. of cases	No. of non-transfers	Rate per 10,000 deliveries[a]
Thanatophoric dysplasia	12	5	0.40
OI type II	9	3	0.24
Campomelic dysplasia	4	2	0.16
Achondroplasia	3	3	0.24
SED congenita	3	3	0.24
Desbuquois syndrome	1	1	0.08
OI type III	2	2	0.16
Achondrogenesis	1	0	0.00
Short rib polydactyly type I (Saldino-Noonan)	1	1	0.08
Short rib polydactyly type II (Majewski)	1	1	0.08
Diastrophic dysplasia	1	0	0.00
Chondrodysplasia punctata (Conradi-Hunerman)	1	0	0.00
Melnick-Needles (Osteodysplasty)	1	1	0.08
Larsen syndrome	1	1	0.08
Cases with no specific diagnosis	8	4	0.32
Totals	49	27	2.14

[a]Based on non-transfer cases.

1979 reportedly at 21 weeks gestation, according to medical record—ultrasound report unavailable for review), a case of heterozygous achondroplasia (ultrasound study in 1982 at 16 weeks at time of amniocentesis), a case of OI type II (ultrasound study in 1985 at 19 weeks gestation for dating purposes), a case of Larsen syndrome (ultrasound study in 1987 at 16 weeks gestation for dating purposes), a case of OI type III (ultrasound study in 1990 at 18 weeks gestation at the time of amniocentesis for elevated maternal serum alpha-fetoprotein), and a non-lethal case in which a specific diagnosis was never made (ultrasound study in 1990 at 13 and 22 weeks for dating purposes and at the time of amniocentesis, respectively).

Osteochondrodysplasias were suspected earlier in pregnancy in more recent years. The mean gestational age when an abnormality was suspected on ultrasound study for the 1979–1984 time period and the 1985–1990 time period were 29.4 weeks and 22.7 weeks, respectively, for all cases, and 29.3 weeks and 21.5 weeks for non-transfers, respectively.

Of the final diagnoses listed in Table II, most were suspected of having an osteochondrodysplasia during pregnancy by ultrasonography. Cases with thanatophoric dysplasia, OI type II, diastrophic dysplasia, spondyloepiphyseal dysplasia (SED) congenita, campomelic dysplasia, chondrodysplasia punctata, achondrogenesis type II, Desbuquois syndrome, and 4 of the patients with unknown diagnoses were suspected of having an osteochondrodysplasia at a gestational age of less than 25 weeks. In addition, an osteochondrodysplasia was suspected in fetuses ultimately diagnosed

TABLE III. Brief Description of BWH Cases Without a Specific Diagnosis

Date of delivery	Birth status	Gestational age (in weeks)	Brief description of clinical/radiographic findings
11/29/80	Neonatal death	36	Disseminated fractures consistent with OI type II with encephalomeningocele and porencephaly
09/15/81	Pregnancy termination-D&E	18	Short upper limbs, hands rotated/supinated, short lower limbs with rotation/supination at ankles—severe fragmentation secondary to termination procedure complicated diagnostic efforts
02/07/84	Stillbirth	35	Short limbs (primarily rhizomelic shortness), bowing of left femur, dysmorphic facies (beaked nose with bulbous tip, hypertelorism), cleft palate
11/24/84	Pregnancy termination-infusion	19	Unusual form of campomelic dysplasia, not previously described
05/05/85	Pregnancy termination-infusion	21	Bowing of femurs, platyspondyly, micrognathia, not compatible with classic campomelic or kyphomelic dysplasia
07/14/85	Neonatal death	38	Preaxial polydactyly, intestinal malrotation with common mesentery, pulmonary hypoplasia, metaphyseal dysplasia, with radiographic and histologic findings consistent with achondroplasia
11/07/85	Pregnancy termination-infusion	20	Unusual form of campomelic dysplasia, not previously described
08/27/90	Liveborn	39	Frontal bossing, large anterior fontanelle, blue sclerae, pectus excavatum, shortening of limbs, bowing of upper limbs, hypoplastic scapulae, dysplastic iliac bones with defects in ossification resembling fractures

TABLE IV. Osteochondrodysplasias (Total and Non-Transfers) Suspected Prenatally by Ultrasonography by Time Period

	Suspected prenatally				Suspected <25 weeks gestation			
	Total cases		Non-transfers		Total cases		Non-transfer	
Time period	n	(%)	n	(%)	n	(%)	n	(%)
1972–1974[a]	0	(0)	0	(0)	0	(0)	0	(0)
1979–1981	4	(50)	2	(33)	1	(13)	1	(17)
1982–1984	9	(90)	2	(67)	3	(30)	0	(0)
1985–1987	11	(85)	7	(88)	8	(62)	5	(63)
1988–1990	12	(80)	4	(57)	6	(40)	2	(29)
Totals	36	(73)	15	(56)	18	(37)	8	(30)

[a]February 16, 1972–February 15, 1975.

with OI type III, short rib polydactyly-Majewski type, Melnick-Needles syndrome, and 2 patients with unknown diagnoses, but not until after 24 weeks gestational age. Although most of the osteochondrodysplasias in our series were suspected on prenatal ultrasonography, diagnosis of specific conditions was difficult. On review of the ultrasound reports, in most cases a description of findings was given without delineation of a specific diagnosis. Often a differential diagnosis or "most likely" diagnosis was given. Of the 29 cases in which an osteochondrodysplasia was suspected on ultrasound study, the ultrasound report was available for review and a final diagnosis was made after delivery, a "most likely" ultrasound diagnosis was given for 17 cases, and this diagnosis was the same as the final clinical/pathology diagnosis in 13 cases.

We reviewed the ultrasound reports for information regarding the amount of amniotic fluid. Polyhydramnios was noted on ultrasound study in 13 of 42 cases (31%) in which ultrasonography had been performed during the second or third trimester. In 2 cases, oligohydramnios was noted on ultrasound study (one of these was following rupture of membranes). In 21 of 42 cases (50%) the amount of amniotic fluid was said to be normal or only slightly increased. In 4 cases amniotic fluid amount was not specifically mentioned in the report, and in 2 cases the ultrasound report was not available for review. The cases with polyhydramnios on ultrasound study included 3 cases of thanatophoric dysplasia, 2 cases of OI type II, 2 cases of campomelic dysplasia, one case each of OI type III, Desbuquois syndrome, and SED congenita, and 3 cases in which no diagnosis was made. In addition, one case with SED congenita was noted to have severe polyhydramnios clinically, but an ultrasound study was not performed. Among the cases in which polyhydramnios was noted by ultrasound, gestational age at the time of ultrasound study ranged from 19 to 36 weeks with a mean of 31.9 weeks. The one patient with polyhydramnios at 19 weeks was noted to have mild polyhydramnios. One patient noted to have a normal amount of amniotic fluid at 22 weeks of gestation was noted to have polyhydramnios at 36 weeks gestation. Of the cases with normal or slightly increased amounts of amniotic fluid noted on ultrasound study, the gestational age at time of the study ranged from 14 to 37 weeks, with a mean of 21.1 weeks.

Birth status was defined for all cases as either liveborn (excluding those babies who died in neonatal period), stillborn, neonatal death (death within the first 28 days of life), and pregnancy termination. Overall, 9 patients (18%) were liveborn, 4 (8%) were stillborn, 20 (41%) were neonatal deaths, and 16 (33%) were pregnancy terminations because of fetal abnormality diagnosed on ultrasound study. Of these, 7 were terminated by evacuation procedures, while 9 were terminated by labor induction. Of those infants dying neonatally, 16 of 20 died in the first day of life, 3 died within the first week, and one died at age 13 days.

Table V shows the change in birth status over the years of our study, related to the increasing second trimester prenatal diagnosis of these conditions. Of the 3 patients born in the early 3 years of our study, one was stillborn and 2 were neonatal deaths. By the final 3-year period (1988–1990), 6 of 15 patients (40%) were pregnancy terminations, while 4 of 15 (27%) were liveborn, 4 of 15 (27%) were neonatal deaths, and one of 15 (7%) was stillborn. Among the 27 non-transfers, 8 (30%) were liveborn, 2 (7%) were stillborn, 11 (41%) were neonatal deaths, and 6 (22%) were pregnancy terminations (Table V). The non-transfers showed a similar trend in change in birth status; the number of cases delivered after a pregnancy termination increased from none during the early 3-year period (1972–1975), to 29% during the final 3 year period (1988–1990). Examination of our data demonstrates that as the proportion of pregnancy terminations increases, the proportion of neonatal deaths and stillborns decreases, but no decrease is seen in liveborn infants surviving more than a month (Table V).

DISCUSSION

The prevalence rate of osteochondrodysplasias in our study is 2.14 cases per 10,000 deliveries. Previous epidemiologic studies on the osteochondrodysplasias have shown a range of rates from 1.1 [Connor et al., 1985] to 7.6 per 10,000 births [Anderson and Hauge, 1989a] (Table VI), reflecting differences in case ascertainment and definition. Our estimate of prevalence of osteochondrodysplasias is similar to estimates from several other studies [Camera and Mastroiacovo, 1982; Orioli et al., 1986; Stoll et al., 1989; Källén et al., 1993]. The rate of lethal osteochondrodysplasias in our study, 0.95 per 10,000 deliveries, is also similar to previous esti-

TABLE V. Birth Status of Osteochondrodysplasias by Time Period

	Liveborns		Stillborns		Neonatal deaths		Pregnancy terminations	
Time period	n	(%)	n	(%)	n	(%)	n	(%)
All cases								
1972–1974[a]	0	(0)	1	(33)	2	(67)	0	(0)
1979–1981	1	(13)	0	(0)	6	(75)	1	(13)
1982–1984	1	(10)	2	(20)	4	(40)	3	(30)
1985–1987	3	(23)	0	(0)	4	(31)	6	(46)
1988–1990	4	(27)	1	(7)	4	(27)	6	(40)
Totals	9	(18)	4	(8)	20	(41)	16	(33)
Non-transfers								
1972–1974[a]	0	(0)	1	(33)	2	(67)	0	(0)
1979–1981	1	(17)	0	(0)	4	(67)	1	(17)
1982–1984	1	(33)	1	(33)	1	(33)	0	(0)
1985–1987	3	(38)	0	(0)	2	(25)	3	(38)
1988–1990	3	(43)	0	(0)	2	(29)	2	(29)
Totals	8	(30)	2	(7)	11	(41)	6	(22)

[a]February 16, 1972–February 15, 1975.

mates [Connor et al., 1985; Andersen, 1989]. The much higher birth prevalence rate determined by Andersen and Hauge [1989a] of 7.6 per 10,000 was based on inclusion of cases identified at any age as having a skeletal dysplasia. In contrast, our study limits cases to those identified in the first 5 days of life, since we had no uniform method of case ascertainment after discharge from BWH. The higher prevalence of 4.7 per 10,000 reported by Gustavson and Jorulf [1975] may be explained by inclusion of high-risk pregnancies in their hospital-based study; however, during the years of their study (1970–1974), prior to the use of prenatal ultrasonography, the rate of referrals from outside hospitals would not be expected to be as high. If our prevalence rate had been based on all patients identified, without excluding transfers, it would have been nearly that noted by Gustavson and Jorulf [1975]. Our study highlights the need for exclusion of high-risk patients referred to a tertiary care center in hospital-based epidemiologic studies.

Our estimate of the prevalence rate of osteochondrodysplasias is likely to underestimate the true rate for 2 reasons. First, some patients with milder osteochondrodysplasias not recognizable in the newborn period clinically or radiographically were missed in our study, since our study limits identification to the first 5 days of life. With the recent practice of earlier hospital discharges of well newborns, the opportunity for diagnosis of milder conditions will become even more limited. Two cases have come to our attention, one with OI type I ascertained in our surveillance system because of cryptorchidism and megalencephaly, and one with hypochondroplasia (usually not diagnosed before 2 years) ascertained because of megalencephaly, which were not recognized as having an osteochondrodysplasia before discharge from the hospital, and are therefore excluded from our data set. Second, our denominator used for rate determination includes all livebirths and stillbirths plus a percentage of pregnancy terminations. The proportion of all mothers transferred to BWH for high-risk care is unknown. While we have excluded transfers from our numerator, we were unable to exclude them from our denominator. This would have increased our estimate of prevalence rate.

The prevalence rates for specific osteochondrodysplasias in our study were similar to those seen in previous reports. The rate for thanatophoric dysplasia from other studies ranges from 0.09 [Orioli et al., 1986] to 0.60 [Camera and Mastroiacovo, 1982] per 10,000, with our estimate being 0.40 per 10,000 deliveries. Martínez-Frías et al. [1988] has found a rate of 0.27 per 10,000 in their population-based study in Spain. The prevalence rate of OI type II in our study was also similar to that found in other population studies. Andersen and Hauge [1989b] in a population-based study have shown a prevalence rate of 0.26 per 10,000 births, similar to that found in ours (0.24 per 10,000 deliveries). When all types of OI recognizable at birth are grouped together, the birth rate appears to range between 0.37 [Camera and Mastroiacovo, 1982] and 0.64 [Stoll et al., 1989] per 10,000, with our estimate being 0.40 per 10,000 deliveries. The prevalence rate of achondroplasia found in other studies ranged from 0.13 [Andersen and Hauge, 1989a] to 0.64 [Stoll et al., 1989] per 10,000, compared to our rate of 0.24 per 10,000 deliveries.

Eight of 49 cases (16%) did not fit into a specific diagnostic category, despite extensive diagnostic efforts. Previous studies have shown similar results; 6 of 53 cases (11%) in one study had either a newly recognized condition or unspecified diagnosis [Camera and Mastroiacovo, 1982], and 34 of 80 cases (42%) had a questionable diagnosis or no specific diagnosis in another study [Orioli et al., 1986]. In a study which included 7 monitoring programs, 21% (ranging in the different programs from 5.5 to 41%) had an unspecified diagnosis [Källén et al., 1993]. Seven percent of cases referred to the International Skeletal Dysplasia Registry for diagnosis had an unclassified skeletal dysplasia [Sharony et al., 1993].

The evaluation of one case without a final diagnosis was limited because of fragmentation after destructive procedure for pregnancy termination. The remainder of

TABLE VI. Summary of Epidemiologic Studies of Osteochondrodysplasias

Reference	Population studied	Type of study	No. of cases	Total population	Rate per 10,000	Years of study
Gustavson and Jorulf, 1975	Osteochondrodysplasias in newborns	Hospital-based	7	14,918 livebirths and stillbirths	4.7	2/70–8/74
Camera and Mastroiacovo, 1982	Skeletal dysplasias in first 7 days of life	Multicenter, hospital-based	53	217,061 livebirths and stillbirths	2.4	1/78–6/81
Connor et al., 1985	Lethal neonatal chondrodysplasias	Population-based	38	337,771 livebirths and stillbirths	1.1	1975–1983
Orioli et al., 1986	Skeletal dysplasias in first 3 days of life	Multicenter, hospital-based (26 hospitals)	80	349,470 livebirths and stillbirths with birth weight ≥ 500 g	2.3	1978–1983
Stoll et al., 1989	Skeletal dysplasias in first 8 days of life	Population-based	34	105,374 livebirths and fetuses ≥ 20 weeks, includes pregnancy terminations	3.2	1979–1986
Andersen, 1989	Lethal osteochondrodysplasias	Population-based	12	77,977 livebirths and stillbirths	1.5	1970–1983
Andersen and Hauge, 1989a	Generalized bone dysplasias—includes diagnoses made later in life	Population-based	59	77,977 livebirths and stillbirths	7.6	1970–1983
Källén et al., 1993	Skeletal dysplasias—age of diagnosis not specified	7 monitoring programs—3 hospital-based, 4 population-based	1500	9,577,000 livebirths and stillbirths (definition and inclusion of stillbirths varied by program)	1.6	1965–1989 (years varied by program)
Present study	Osteochondrodysplasias in first 5 days of life	Hospital-based—patients transferred for high risk care excluded	27	126,316 livebirths, stillbirths, includes pregnancy terminations	2.1	2/16/72–2/15/75, 1979–1990
	Lethal cases only		12		0.95	

our cases without a final diagnosis presented patterns of malformation which have not been described previously. For example, one infant, born to parents who were first cousins, had bone abnormalities consistent with osteogenesis imperfecta congenita with an encephalocele, which may represent a previously undescribed autosomal recessive condition.

The use of prenatal ultrasonography has altered the birth status of cases of osteochondrodysplasias; more frequently in recent years these cases are the products of pregnancy terminations after ultrasonographic identification. The challenge to clinical geneticists, radiologists, and pathologists in making an accurate diagnosis and providing appropriate genetic counseling to affected families has increased, since this trend has made diagnosis by traditional clinical means more difficult, and in some cases impossible. Radiographic studies continue to be valuable, because postmortem radiographs of the fetus may be helpful, even after destructive pregnancy termination procedures. In addition, biochemical and molecular techniques, which were not included as part of our case evaluation, have recently been identified as useful in diagnosis of some osteochondrodysplasias [Byers, 1989, 1993; Hastbacka et al., 1993, 1994; Tilstra and Byers, 1994; Spranger et al., 1994; Shiang et al., 1994; Rousseau et al., 1994; McIntosh et al., 1994; Bellus et al., 1995; Briggs et al., 1995; Hecht et al., 1995]. Utilization of these techniques has the potential for assisting in the specific diagnosis of cases of osteochondrodysplasias, and could allow for earlier and more accurate prenatal diagnosis in future pregnancies.

Our study demonstrates that while the proportion of pregnancy termination cases increases, the proportion of stillbirths and neonatal deaths decreases, but the proportion of liveborns surviving more than a month has not decreased. From an epidemiologic viewpoint, the use of prenatal diagnosis in the osteochondrodysplasias may prevent the delivery of a stillborn infant or of an infant destined for early death, but does not appear to change the frequency of delivery of liveborns likely to survive more than a month.

Ultrasonographic evaluation had been performed during the second or third trimester in a high proportion (42/49 or 86%) of cases. All cases of lethal osteochondrodysplasias in which an ultrasound evaluation was performed during the second/third trimester were prenatally suspected of having an osteochondrodysplasia, except for a case of thanatophoric dysplasia and a case of OI type II, delivered in 1979 and 1985, respectively. The reason why these lethal diagnoses were missed is unclear, but the early year and indication may be related. In addition, specific criteria for ultrasound diagnosis of an osteochondrodysplasia were not utilized in this study, since the ultrasonographic studies had been performed by different ultrasonographers with varying degrees of expertise using different equipment and during disparate time periods.

Although an osteochondrodysplasia was suspected in a high proportion of our cases by prenatal ultrasonography, a specific diagnosis was difficult. Part of the difficulty in our series may be due to the fact that we reviewed ultrasound reports from multiple sources. However, the challenge in making a specific ultrasound diagnosis has been previously recognized. In a series reported by Sharony et al. [1993], the specific ultrasound diagnosis was incorrect in over half of the 226 fetuses referred to their International Skeletal Dysplasia Registry. Findings on ultrasonography often are not pathognomonic of a particular osteochondrodysplasia [Donnenfeld and Mennuti, 1987] and it is difficult to get an integrated view of the fetus [Vandenburghe et al., 1984]. The model protocol to assist in the prenatal ultrasound diagnosis of the skeletal dysplasias, proposed by Escobar et al. [1990], does not provide a specific diagnosis in most cases; instead, their protocol provides a differential of 2 to 10 diagnoses. Some authors have suggested that measurements of the thoracic cage may be helpful in determining which fetuses have lethal conditions [Romero et al., 1989; Lachman and Rappaport, 1990] because the cause of death in many of these infants is respiratory distress related to lung hypoplasia. In addition, prenatal radiographs may be important in helping delineate the diagnosis of a fetus found to have short limbs or at least to help distinguish lethal conditions [Sharony et al., 1993]. More research aimed at methods of precise ultrasonographic diagnosis is needed. In addition, sonographic findings always need to be confirmed, either by pathology studies after pregnancy termination, or with careful postnatal clinical examination and radiography [Winter et al., 1988; Lachman, 1994].

A large proportion of our cases of osteochondrodysplasia had polyhydramnios, an association which has been previously recognized [Wong and Filly, 1983; Connor et al., 1985; McGuire et al., 1987]. Later ultrasound studies were more likely to document polyhydramnios than earlier ones. Polyhydramnios, seen in about 1% of pregnancies, has numerous causes [Wallenburg and Wladimiroff, 1977]; however, when it is observed, an osteochondrodysplasia should be considered.

The increasing use of prenatal ultrasound has changed the surveillance of osteochondrodysplasias. Ours is the first epidemiologic study of osteochondrodysplasias which includes a significant number of pregnancy terminations. In Stoll's study published in 1989, 4 of 34 cases (12%) with skeletal dysplasias were pregnancy terminations, in contrast to about a third of cases in our study. Their exclusion from our study would have suggested a downward trend in the prevalence of this condition. In a previous study [Källén et al., 1993], changes in prevalence rates were partially explained by prenatal diagnosis followed by pregnancy termination; however, the number of these termination cases was not known. A trend in changing birth status due to prenatal recognition similar to that seen in the osteochondrodysplasias was observed in a study of anencephaly, also performed at BWH [Limb and Holmes, 1994]. In that study, the changes in the proportion of prenatally detected cases and in birth status were even more dramatic (100% of cases were detected prenatally and all pregnancies were terminated by the year 1990). These findings emphasize the impact that prenatal identification may have on the epidemiology of conditions which

are diagnosed prenatally, an important consideration in the design of future epidemiologic studies.

In summary, we have presented a review of the osteochondrodysplasias seen at a large teaching hospital over a 15-year period. Our data demonstrate that the presentation of these conditions is changing because of the availability of prenatal ultrasonography, with most fetuses now being identified prenatally. Ultrasound study appears to be an excellent mode of identifying fetuses with short limbs and other abnormalities, and the capability now exists to identify nearly all lethal osteochondrodysplasias; however, making an exact diagnosis is often difficult. In addition, it is often difficult to make a specific diagnosis even after birth or pregnancy termination. The increased frequency of pregnancy terminations, in particular those by destructive methods, makes the diagnosis based on traditional clinical methods more difficult and in some cases impossible. The promise for the future in this area is the inclusion of biochemical and molecular investigations which already in some cases serve as an adjunct to the traditional clinical, pathology, and radiographic studies. This will allow for more families to be provided with precise diagnoses and accurate recurrence risk information.

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